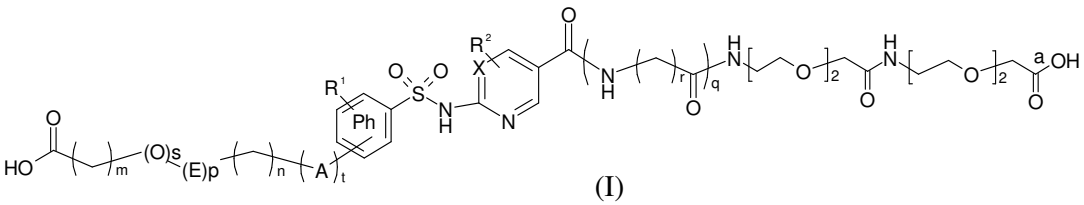
~~Claims~~

CLAIMS

1. A conjugate comprising an insulin analog and a sulfonamide of formula (I)



(I)

wherein:

A is selected from the group consisting of oxygen atom, -CH_2CH_2- group, -OCH_2- group and -CH_2O- group;

E represents a -C_6H_3R- group with R being a hydrogen atom or a halogen atom, wherein the halogen atom is selected from the group consisting of fluorine, chlorine, bromine and iodine atom;

X represents a nitrogen atom or a -CH- group;

m is an integer in the range from 5 to 17;

n is zero or an integer in the range from 1 to 3;

p is zero or 1;

q is zero or 1;

r is an integer in the range from 1 to 6;

s is zero ~~or 1~~;

t is zero or 1;

R^1 represents at least one residue selected from the group of hydrogen atom, halogen atom, C1 to C3 alkyl group and halogenated C1 to C3 alkyl group;

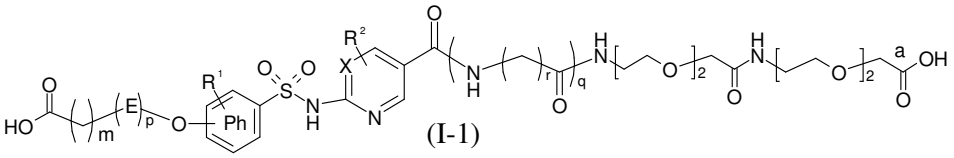
R^2 represents at least one residue selected from the group of hydrogen atom, halogen atom, C1 to C3 alkyl group and halogenated C1 to C3 alkyl group,

wherein the insulin analog is an analog of human insulin,

wherein the sulfonamide of formula (I) is covalently bound to the insulin analog in that terminal carboxy group “a” of the sulfonamide of formula (I) is covalently bound ~~to an amino group to of the insulin analog~~the epsilon amino group of a

lysine present in the insulin analog or the N-terminal amino group of the B chain of the insulin analog.

2. The conjugate according to claim 1, wherein the sulfonamide has the formula (I-1)



(I-1)

wherein:

E represents a $-C_6H_3R-$ group with R being a hydrogen atom or a halogen atom, wherein the halogen atom is selected from the group consisting of fluorine, chlorine, bromine and iodine atom;

X represents a nitrogen atom or a –CH- group;

p is zero or 1;

q is zero or 1;

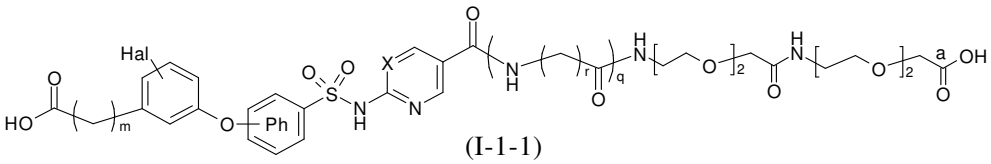
r is an integer in the range from 1 to 6;

R^1 represents at least one residue selected from the group of hydrogen atom and halogen atom;

R^2 represents at least one residue selected from the group of hydrogen atom, C1 to C3 alkyl group and halogenated C1 to C3 alkyl group;

with m being an integer in the range from 5 to 15 if p is zero, or m being an integer in the range from 7 to 15 if p is 1.

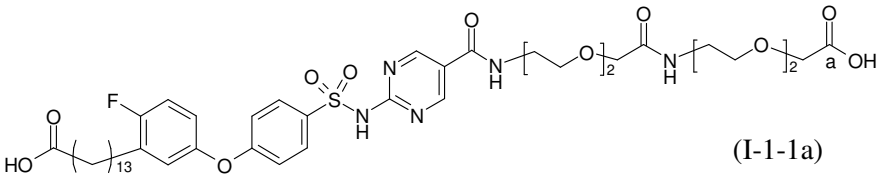
3. The conjugate according to claim 1 or 2, wherein the sulfonamide has the formula (I-1-1)



(I-1-1)

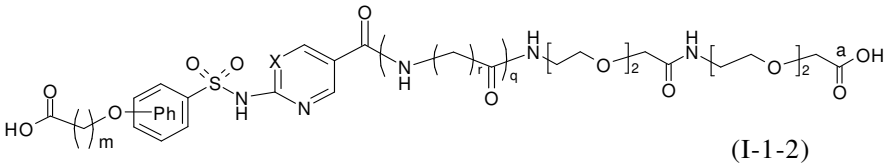
wherein X is a nitrogen atom or a –CH- group; m is an integer in the range from 7 to 15; r is an integer in the range from 1 to 6; q is zero or 1; Hal is a halogen atom selected from the group consisting of fluorine, chlorine, bromine and iodine atom; and the $HOOC-(CH_2)_m-C_6H_3Hal-O-$ group is situated in meta or para position on phenyl ring Ph with respect to the $-S(O)_2-$ group.

4. The conjugate according to any of claims 1 to 3, wherein the sulfonamide has the formula (I-1-1a)



(I-1-1a)

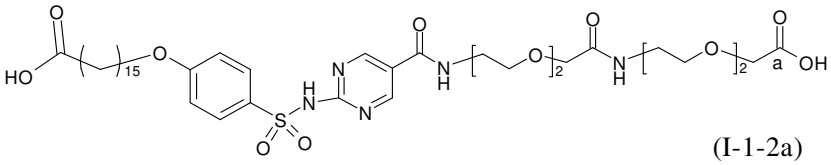
5. The conjugate according to claim 1 or 2, wherein the sulfonamide has the formula (I-1-2)



(I-1-2)

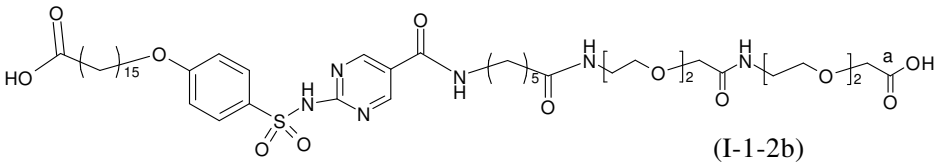
wherein X is a nitrogen atom or a -CH- group; m is an integer in the range from 5 to 15; r is an integer in the range from 1 to 6; q is zero or 1; and the HOOC-$(CH_2)_m$-O- group is situated in meta or para position on phenyl ring Ph with respect to the -$S(O)_2$- group.

6. The conjugate according to any of claims 1 to 2 or 5, wherein the sulfonamide has the formula (I-1-2a)



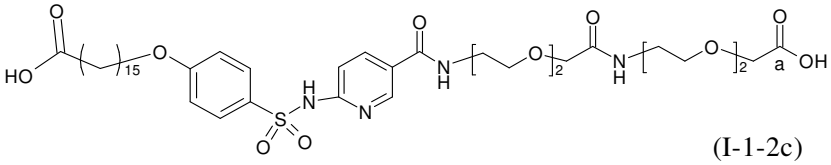
(I-1-2a)

or the formula (I-1-2b)



(I-1-2b)

or the formula (I-1-2c)



(I-1-2c)

7. The conjugate according to any one of claims 1 to 6, wherein the insulin analog comprises at least one mutation relative to ~~the parent~~human insulin, wherein the insulin analog comprises a mutation at position B16 which is substituted with a hydrophobic amino acid and/or a mutation at position B25 which is substituted with a hydrophobic amino acid, and optionally, wherein said insulin analog further comprises a mutation at position A14 which is substituted with an amino acid selected from the group consisting of glutamic acid (Glu), aspartic acid (Asp) and histidine (His) and/or a mutation at position B30.

8. The conjugate according to claim 7, ~~wherein the parent insulin is human insulin, porcine insulin, or bovine insulin, and/or~~ wherein the hydrophobic amino acid is a branched-chain amino acid, such as a branched-chain amino acid selected from the group consisting of valine (Val), isoleucine (Ile), and leucine (Leu).

9. The conjugate according to any one of claims 1 to 8, wherein the insulin analog is selected from
Leu(B16)-human insulin,
Val(B16)-human insulin,
Ile(B16)-human insulin,
Leu(B16)Des(B30)-human insulin,
Val(B16)Des(B30)-human insulin,
Ile(B16)Des(B30)-human insulin,
Leu(B25)-human insulin,
Val(B25)-human insulin,
Ile(B25)-human insulin,
Leu(B25)Des(B30)-human insulin,
Val(B25)Des(B30)-human insulin,
Ile(B25)Des(B30)-human insulin,
Glu(A14)Leu(B16)Des(B30)-human insulin,
Glu(A14)Ile(B16)Des(B30)-human insulin,
Glu(A14)Val(B16)Des(B30)-human insulin,
Glu(A14)Leu(B16)-human insulin,
Glu(A14)Ile(B16)-human insulin,

Glu(A14)Val(B16)-human insulin,
Glu(A14)Leu(B25)Des(B30)-human insulin,
Glu(A14)Ile(B25)Des(B30)-human insulin,
Glu(A14)Val(B25)Des(B30)-human insulin,
Glu(A14)Leu(B25)-human insulin,
Glu(A14)Ile(B25)-human insulin,
Glu(A14)Val(B25)-human insulin,
Glu(A14)Gly(A21)Glu(B3)Val(B25)Des(B30)-human insulin,
Glu(A14)Ile(B16)Ile(B25)Des(B30)-human insulin,
Glu(A14)Glu(B3)Ile(B16)Ile(B25)Des(B30)-human insulin,
Glu(A14)Ile(B16)Val(B25)Des(B30)-human insulin,
Glu(A14)Gly(A21)Glu(B3)Ile(B16)Val(B25)Des(B30)-human insulin,
Glu(A14)Val(B16)Ile(B25)Des(B30)-human insulin,
Glu(A14)Val(B16)Val(B25)Des(B30)-human insulin,
Glu(A14)Glu(B3)Val(B16)Val(B25)Des(B30)-human insulin,
Glu(A14)Gly(A21)Glu(B3)Val(B16)Val(B25)Des(B30)-human insulin,
Glu(A14)Gly(A21)Glu(B3)Val(B25)-human insulin,
Glu(A14)Ile(B16)Ile(B25)-human insulin,
Glu(A14)Glu(B3)Ile(B16)Ile(B25)-human insulin,
Glu(A14)Ile(B16)Val(B25)-human insulin,
Glu(A14)Gly(A21)Glu(B3)Ile(B16)Val(B25)-human insulin,
Glu(A14)Val(B16)Ile(B25)-human insulin,
Glu(A14)Val(B16)Val(B25)-human insulin,
Glu(A14)Glu(B3)Val(B16)Val(B25)-human insulin, and
Glu(A14)Gly(A21)Glu(B3)Val(B16)Val(B25)-human insulin.

10. The conjugate according to any one of claims 1 to 9, wherein the insulin analog comprises

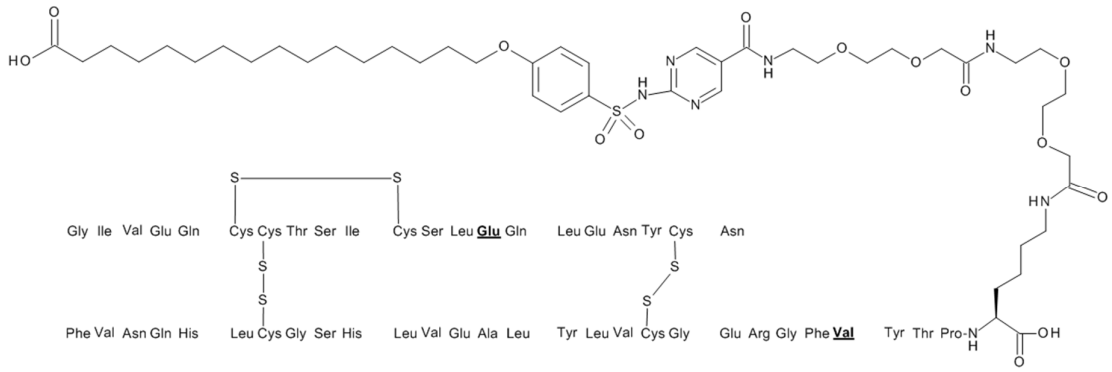
(a) an A chain having an amino acid sequence as shown in SEQ ID NO: 43 (GIVEQCCTSICSLEQLENYCN) and a B chain having an amino acid sequence as shown in SEQ ID NO: 44 (FVNQHLCGSHLVEALYLVCGERGFIYTPK),

(b) an A chain having an amino acid sequence as shown in SEQ ID NO: 47 (GIVEQCCTSICSLEQLENYCN) and a B chain having an amino acid sequence as shown in SEQ ID NO: 48 (FVNQHLCGSHLVEALYLVCGERGFVYTPK), or

(c) an A chain having an amino acid sequence as shown in SEQ ID NO: 77 (GIVEQCCTSICSLEQLENYCN) and a B chain having an amino acid sequence as shown in SEQ ID NO: 78 (FVEQHLCGSHLVEALVLVCGERGFVYTPK).

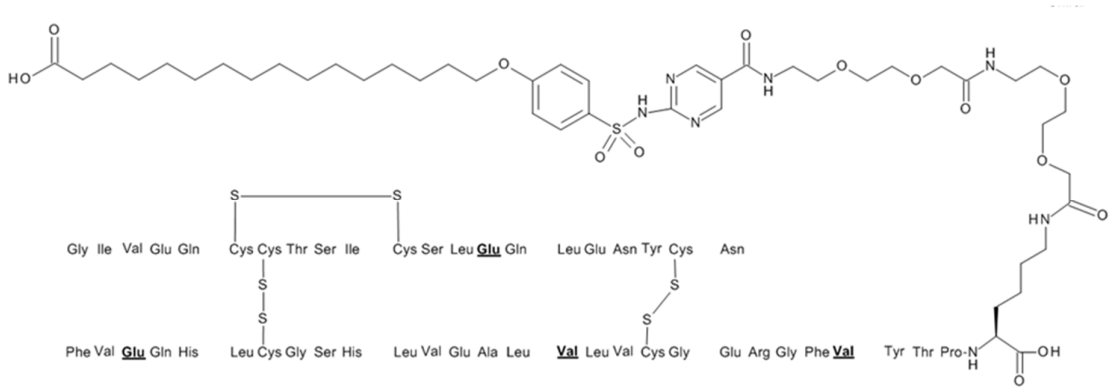
11. The conjugate of any one of claims 1 to 10, wherein the amino group of the insulin analog, to which the sulfonamide of formula (I) is covalently bound, is ~~an epsilon amino group of a lysine present in the insulin analog or is the N-terminal amino group of the B-chain of the insulin or insulin analog, e.g. wherein the amino group is~~ the epsilon amino group of lysine present at position B29 of the B chain.

12. The conjugate of any one of claims 1 to 11, wherein the conjugate is conjugate 1 (A chain sequence: SEQ ID NO: 47; B chain sequence: SEQ ID NO: 48):



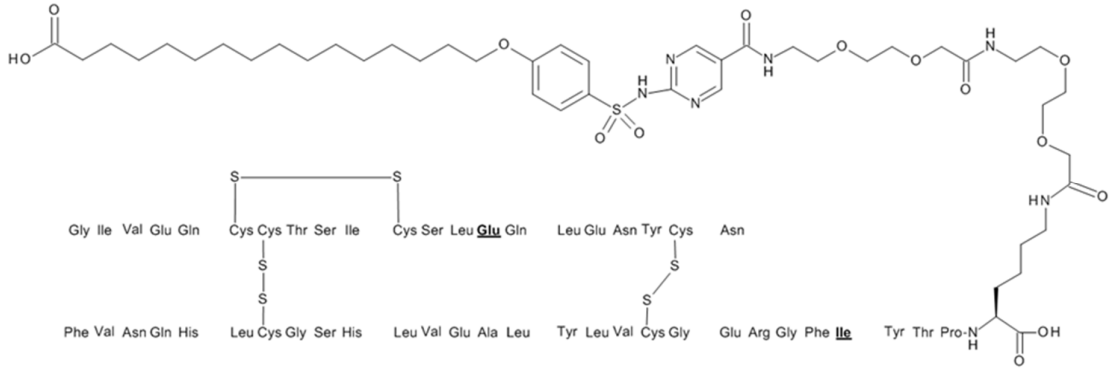
or

conjugate 3 (A chain sequence: SEQ ID NO: 77; B chain sequence: SEQ ID NO: 78):



or

conjugate 4 (A chain sequence: SEQ ID NO: 43; B chain sequence: SEQ ID NO: 44):



13. Pharmaceutical composition comprising in a pharmaceutically effective amount the conjugate comprising a sulfonamide of formula (I) and an insulin analog according to any of claims 1 to 12.

14. The conjugate comprising a sulfonamide of formula (I) and an insulin analog according to any of claims 1 to 12 for use as a medicament.

15. The conjugate comprising a sulfonamide of formula (I) and an insulin analog according to any of claims 1 to 12 for use as a medicament for treatment of a disease selected from the group consisting of gestational diabetes, diabetes mellitus type 1, diabetes mellitus type 2, and hyperglycemia and/or for lowering blood glucose levels.